Atomic structure of a toxic, oligomeric segment of SOD1 linked to amyotrophic lateral sclerosis (ALS).

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Public Summary:
More than 170 mutations in superoxide dismutase 1 (SOD1) are linked to inherited forms of ALS, and aggregates of this protein are a pathological feature associated with this disease. Although it is accepted that SOD1 gains a toxic function in the disease state, a molecular understanding of the toxic species is lacking. Here, we identify a short segment of SOD1 that is both necessary and sufficient for toxicity to motor neurons. The crystal structure of the segment reveals an out-of-register β-sheet oligomer, providing a structural rationale for the toxic effects of mutant SOD1 in ALS.

Scientific Abstract:
Fibrils and oligomers are the aggregated protein agents of neuronal dysfunction in ALS diseases. Whereas we now know much about fibril architecture, atomic structures of disease-related oligomers have eluded determination. Here, we determine the corkscrew-like structure of a cytotoxic segment of superoxide dismutase 1 (SOD1) in its oligomeric state. Mutations that prevent formation of this structure eliminate cytotoxicity of the segment in isolation as well as cytotoxicity of the ALS-linked mutants of SOD1 in primary motor neurons and in a Danio rerio (zebrafish) model of ALS. Cytotoxicity assays suggest that toxicity is a property of soluble oligomers, and not large insoluble aggregates. Our work adds to evidence that the toxic oligomeric entities in protein aggregation diseases contain antiparallel, out-of-register beta-sheet structures and identifies a target for structure-based therapeutics in ALS.